tropicalis; *C. glabrata*+*C. kefyr* and those with 3 *Candida* species colonization.
Conclusions: This casual relationship between prominent *Candida* colonization and adverse impact on short-term mortality especially, in patients with hematological cancer and BMT recipients was not surprising. High mortality in patients with *C. glabrata* and *C. krusei* multiple sites and/or multiple species colonization was documented.

Invasive aspergillosis with predominant thyroid and myocardial involvement

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Invasive aspergillosis (IA) is a common fungal infection in immunocompromised patients with a high mortality rate. We report the case of a 49-year old man with history of fever and chills 4 months after kidney transplantation. Physical examination and chest radiography were normal. Laboratory tests showed CRP elevation (78 mg/l). Blood cultures and urine bacteriology were sterile. Cytomegalovirus-antigenemia negative. Computed tomography (CT) of the chest discluded a small nodular lesion (1,2 cm) in the left lower lobe. No pathogenic organism was identified by bronchoalveolar lavage. Serology for toxoplasmosis and cryptococcal antigen were negative. Control CT of the chest 2 weeks later revealed minimal progression of the pulmonary lesion and an in-homogenous enlargement of the thyroid gland. Fine needle aspiration of the thyroid revealed growth of *Aspergillus fumigatus*. Inspite of anti-fungal therapy with liposomal Amphotericin B the patient remained febrile. Echocardiography and MRI of the heart showed fibrotic pericarditis and several myocardial abscesses, suggesting disseminated IA. Caspofungin and flucytosine was added to amphotericin B. Flucytosine was stopped after 2 weeks because of leukopenia. Three months after the therapy of amphotericin B and caspofungin, we observed favourable clinical course, regression of the pulmonary lesions and vanishing of the myocardial abscesses. The patient was discharged on oral itraconazole. In conclusion, we report an unusual clinical presentation of invasive aspergillosis with multiple myocardial abscesses in an immunocompromised patient with favourable outcome under experimental antifungal combination therapy.

Yeasts in patients (PTS) with hematologic malignancies (HM)

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Objectives: To receive a database, which is a basis for realization of effective preventive and empiric therapy of severe fungal infections in PTS with HM.

Methods: The monitoring for selection of yeasts from different samples (urine, throat, blood, stool and others) during 2000–01 was performed. The standard techniques of microbiological research were used. The strains were identified by the selective medium (CROMagar, Becton Dickinson), "Auxacolor" (BIO-RAD) too. Susceptibility tests to antifungal drugs (6 agents) were performed with "Fungitest" (BIO-RAD). In our study BACTEC 9050 blood culture system (Becton Dickinson Diagnostic instrument Systems) was used (Blood specimens were inoculated into BACTEC Mycosis-IC/F).
Results: A total of 590 strains from 294 PTS with HM between 2000 and 2001 were obtained. From 316 samples fungi were isolated in 8.9 % of cases in association (more than one strain from the same sample). 21 positive blood cultures from 14 PTS were obtained (only *Candida* spp., 64% of them were non-albicans *Candida* species). There were 3 genera of yeasts in our hospital. Among them *Candida* spp, *Geotrichum* spp., *Saccharomyces* spp.. *Candida* spp represented 93.7% of all yeast isolates (*C. albicans* – 67.3%, *C. glabrata* – 8.2%, *C. inconspicua* – 7.0%, *C. kefur* – 3.1%, *C. tropicalis* – 2.9%, *C. parapsilosis* – 2.7%, *C. krusei* – 0.9%, *C. lusitaniae* – 0.7%, *C. rugosa* – 0.4%, *C. lipolytica* – 0.2%). Non-albicans *Candida* species represented 28.2% of all *Candida* spp. We performed susceptibility tests of yeasts. No strain of yeasts was resistant to amphotericin B. Susceptibility testing of fungi revealed that the majority of the strains were sensitive to fluconazole, itraconazole, ketoconazole, miconazole, 5-fluorocytosine.
Conclusion: The results of this study demonstrate that the predominant pathogens were *Candida* spp.. All strains of yeasts were susceptible to amphotericin B.

In vitro susceptibility of clinical isolates of *Aspergillus fumigatus* to conventional and lipid formulations of amphotericin B in 2-drug combination with caspofungin and micafungin

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We investigated the in vitro susceptibility of *Aspergillus fumigatus* to 2-drug combination of amphotericin B lipid complex (ABLC) and liposomal amphotericin B (L-AMB) with caspofungin (CFG) and micafungin (MFG), and the results were compared with those obtained for pair-wise combination of conventional amphotericin B (C-AMB) with CFG and MFG. Conidial suspensions were prepared from 20 clinical isolates of *A. fumigatus* (Microbiology Laboratory, Detroit Medical Center, Detroit, Michigan) susceptible to ABLC (MIC 1.26±1.14 μg/mL), L-AMB (MIC 1.9±0.87 μg/mL) C-AMB (MIC 1 (0.0 μg/mL), and CFG (MIC 64±0.0 μg/mL) and MFG (MIC 217.6±61.82 μg/mL). The in vitro susceptibility of

A. fumigatus to 2-drug combination of ABLC, L-AMB or C-AMB with CFG and MFG was evaluated by the fractional inhibitory concentration index (FICI) method. The FICI was determined by a 2-dimensional checker-board using the M38-P broth microdilution technique proposed by the National Committee for Clinical Laboratory Standards for MIC testing of conidium-forming filamentous fungi except that the MIC was defined as the concentration of the drug that provided no visible growth as determined by the reduction of tetrazolium compound (MTT assay). The FICI was calculated by the formula: FICI=(A_c (A_a)+($B_c \div B_a$) where A_c and B_c are the MICs of drugs A and B in combination and A_a and B_a are the MICs of drugs A and B. The drug interactions were classified as synergistic (FICI≤0.5), additive (FICI>0.5 but ≤1), indifferent (FICI>1 but ≤2) and antagonistic (FICI>2). The FICIs obtained for six two-drug combinations were as follows: AMB+CFG=0.42±0.12, ABLC+CFG=0.33±0.15, L-AMB+CFG=0.51±0.10, AMB+MFG=0.51±0.11, ABLC +MFG=0.47±0.15 and L-AMB+MFG=0.43±0.14 indicating synergistic interactions in all six combinations. These in vitro data suggest that conventional and lipid formulations of amphotericin B in 2-drug combination with the echinocandin caspofungin or micafungin is synergistically active against *A. fumigatus*.

Comparison of *Aspergillus nidulans* and *Aspergillus fumigatus* as causes of osteomyelitis in patients with chronic granulomatous disease

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Chronic granulomatous disease (CGD) is a rare inherited disorder of the NADPH oxidase complex in which neutrophils and monocytes fail to generate reactive oxidants such as superoxide anion and hydrogen peroxide, key elements in host defense against a variety of bacterial and fungal pathogens.

The overall incidence of fungal infections in CGD has been reported at least 20%, with *Aspergillus* spp. being responsible for 78% of all fungal infections. Aspergillosis is the most common cause of mortality in these patients being responsible for over one third of deaths. Although *Aspergillus fumigatus* is by far the most frequent fungus causing infections in immunocompromised patients, *A. nidulans* has also been recognized as a human pathogen. Osteomyelitis has occurred in 25% of patients with CGD. *Aspergillus* spp. are the second most common cause accounting for approximately 22% of all osteomyelitis cases as recorded in the USA registry.

We recently treated a CGD patient with femoral osteomyelitis due to *A. nidulans* who had a favorable outcome. We review the reported cases of osteomyelitis in CGD patients due to this organism and we compare them with those due to *A. fumigatus*.

Twenty cases of *A. nidulans* infections have been reported in CGD patients to date. In the great majority, lungs have been involved, whereas in some patients, expansion to neighboring tissues or to remote areas has taken place. Fifteen cases of osteomyelitis due to *A. nidulans* have been described in patients with CGD. All of them have been males and associated with simultaneous pulmonary infection except for our case. Vertebrae and ribs have been found as the sites most commonly affected mainly as a result of rapid contiguous spread from a pulmonary focus. The outcome has been generally poor with a mortality rate approaching 50%. The commonest genetic pattern has been X-linked CGD gp91-phox-deficient (60% of 15 cases). The management of these cases has been problematic. Treatment has required a combined approach with surgical debridement, because of the persistent nature of the organism, and administration of intensive and prolonged antifungal therapy with amphotericin-B (AMB) in the great majority of cases. The addition of a colony-stimulating factor or interferon-gamma has appeared to have catalytic role in the treatment of these infections.

By comparison, osteomyelitis due to *A. fumigatus* has been reported in 8 male CGD patients to date. There has been no predilection for particular bones; tibia, femur, spine and cranium have been some examples. At least two multifocal osteomyelitis cases have been described. In all cases the outcome has been favourable. However, in most of them treatment has required a combined approach with surgical debridement and AMB. In some cases, interferon-gamma has also been used.

In conclusion, overall *A. fumigatus* has been a more common pathogen compared with *A. nidulans* in CGD, but *A. nidulans* has been more virulent and significantly more likely to result in death, to involve adjacent bones and to cause disseminated disease compared to *A. fumigatus*. Patients with *A. nidulans* osteomyelitis have received longer courses of AMB therapy compared to patients with *A. fumigatus* osteomyelitis. Surgical debridement appears to be necessary, but especially in *A. nidulans* osteomyelitis early surgery is imperative. Adjunctive use of cytokines in both *A. nidulans* and *A. fumigatus* osteomyelitis seems to be successful. This comparison shows that *A. nidulans* osteomyelitis carries more severe implications than that of *A. fumigatus* and needs more aggressive therapy.

Antifungal efficacy, pharmacokinetics and pharmacodynamics of intravenous itraconazole against invasive pulmonary aspergillosis in persistently neutropenic rabbits

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